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Clinical paper

Ventricular fibrillation waveform characteristics of the surface ECG: Impact of the left ventricular diameter and mass



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ABSTRACT

Background: Despite a promising association between VF waveform characteristics and prognosis after resuscitation, studies with VF-guided treatment have so far not improved outcomes. While driven by the idea that the VF waveform reflects arrest duration, increasing evidence suggests that pre-existent disease-related changes of the myocardium affect ECG-characteristics of VF as well. In this context, we studied the impact of the left ventricular (LV) diameter and mass.

Methods: Cohort of 193 ICD-patients with defibrillation testing at the Radboudumc (2010–2014). Surface ECG-recordings (leads I,II,aVF,V1,V3,V6) were analysed to study amplitude and frequency characteristics of the induced VF. Both for LV diameter and mass, patients were categorised in two groups, using echocardiographic data (ASE-guidelines).

Results: In all ECG-leads, dominant and median frequencies were significantly lower in patients with (n=40) than in patients without (n=151) an increased LV diameter. The mean amplitude and amplitude spectrum area (AMSA) did not differ. In contrast, we observed no differences in frequency characteristics in relation to the LV mass, whereas mean amplitude (I,aVF,V3) and AMSA (I,V3) were significantly higher in patients with (n=57) than in patients without (n=120) an increased LV mass.

Conclusions: Frequency characteristics of VF were consistently lower in case of an increased LV diameter. Whereas LV mass does not affect the frequency of the VF waveform, amplitudes seem higher with increasing mass. These findings add to the current knowledge of factors that modulate VF characteristics of the surface ECG and provide insight into factors which may be accounted for in future studies on VF-guided resuscitative interventions.

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Introduction

Over the years, various initiatives have been taken to improve outcome after out-of-hospital cardiac arrest (OHCA) [1,2]. For patients with ventricular fibrillation (VF), one of the proposed strategies involves guidance of chest compressions and shock deliveries based on analysis of the VF waveform [2–5].

This idea was based on early observations that the VF waveform of the electrocardiogram (ECG) reflects arrest duration, and evolves from coarse to fine with worsening of the myocardial metabolic state [6]. In this context, it has been thought that patients with longer arrest durations may benefit from a chest compression-first strategy, instead of immediate shock therapy, to improve myocardial readiness for defibrillation [3–5,7]. However, randomised studies comparing these strategies in the OHCA setting, whether or not guided by VF analysis, could not substantiate survival benefit [8,9].

More recent evidence indicates that the appearance of the VF waveform of the surface ECG not only reflects arrest duration, but is also affected by the underlying cardiac disease [10–12]. In animals, VF frequency characteristics have consistently been shown to

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be lower in the presence than in the absence of an acute myocardial infarction (MI) [10,11]. In contrast, studies in OHCA-patients yielded inconsistent results with regard to the impact of an acute MI [13–15]. Besides acute factors, there is robust evidence in both patients and animals that pre-existent cardiac disease affects VF characteristics as well [12,16–18]. Previous studies primarily investigated the impact of infarction, while there is scarcity of data on the effect of other pre-existent disease-related changes of the myocardium on VF characteristics [16–18].

Improved understanding of factors that influence the appearance of the VF waveform of the surface ECG may help to unravel whether and how VF analysis could be helpful to guide resuscitative interventions. In this context, we studied induced VF characteristics of the surface ECG in relation to the left ventricular (LV) diameter and mass in patients who underwent implantable cardioverter defibrillator (ICD) implantation.

Methods

Patient population

From a registry of first ICD implantations at the Radboud University Medical Center, we identified all patients who underwent defibrillation testing from June 2010–January 2014. We included patients for whom the following was available: 1) A 12-lead surface ECG of the induced VF; 2) A complete echocardiographic assessment prior to ICD implantation. Exclusion criteria were: age <18 years, congenital heart disease and right-sided ICD implants. Given the observational design of the study, written informed consent was not necessary to obtain according to the Dutch Act on Medical Research involving Human Subjects.

ICD implantation and testing

The devices implanted were Medtronic (Minneapolis, Minn, USA), St Jude Medical (St. Paul, Minn, USA) or Biotronik (Berlin, Germany) ICD or cardiac resynchronisation therapy-defibrillator systems with transvenous single coil leads. Routine defibrillation testing was performed after ICD implantation to test the ability of the implanted device to sense, detect and terminate VF appropriately. After sedation with propofol, VF was induced using T-wave shock, direct current pulses or 50 Hz burst pacing. The presence of VF, defined as a rapid (around 300 bpm) grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology and amplitude, was confirmed on surface ECG recordings [19]. The ICD was programmed to deliver sequential shocks (15–25–35 J) until VF was terminated. In case of persisting VF after the third shock, an external defibrillation shock was delivered.

Clinical and echocardiographic parameters

Data regarding demographics and medical histories were collected from patient records. The underlying cardiac aetiology was determined using patient charts. In the presence of a previous MI, we crosschecked the MI localisation using ECGs and imaging reports (i.e. echo, nuclear scan, MRI), as described previously [18].

LV diameter and mass

Echocardiographic measurements of the LV internal diastolic diameter (LVIDd) and mass were collected from imaging reports. Both measurements had been done as part of the work-up for ICD implantation according to local standards. Measurements were indexed to body surface area and categorised using gender-specific thresholds as recommended by the American Society of Echocardiography [20]. Echocardiography had to be performed within one

year before ICD implantation and without intercurrent cardiac events.

VF waveform characteristics

ECG recordings

During defibrillation testing, a standard 12-lead ECG of the induced VF was recorded (sampling frequency 1000 Hz; 16-bit A/D converter) with BARD LabSystem Pro (Lowell, Massachusetts, USA). Lead I, II, aVF, V1, V3 and V6 were selected for VF analysis, as these represent the main electrical vectors and include uni- and bipolar leads.

VF waveform analysis

VF waveform characteristics were determined using a time segment of 4.1 s prior to first shock delivery (4096 time-points). The signal was pre-processed with a 2 Hz high-pass filter and a 20 Hz low-pass filter. We analysed several previously studied VF characteristics [5,21,22]. From the ECG-signal in the time domain, we determined the mean absolute amplitude. Subsequently, the signal was converted to the frequency domain by using a fast Fourier transform to visualize the frequencies and corresponding amplitudes, which the sampled VF signal contains [5]. From the amplitude frequency spectrum, the amplitude spectrum area (AMSA) was calculated as the summed product of individual frequencies and their corresponding amplitudes over an interval of 2–20 Hz [21,22]. From the power spectrum, we determined the dominant frequency, which is the frequency where the power spectrum attains its maximum [5]. In addition, we determined the median frequency, i.e. the frequency for which the integrated signal power was one half of the total integrated power. Finally, we calculated the bandwidth, which is the difference in frequency corresponding to the first and third quartile of the total power, providing a measure of the spread in frequencies [22]. Definitions of the analysed VF characteristics are described in detail in the Appendix. Calculations were performed using Matlab (version 2011a, Mathworks, Natick, MA, USA).

Outcome measures and definition of study groups

Outcome measures are the VF waveform characteristics as described above. For analyses on the LV diameter, we compared two groups: 1) patients with normal LV diameters or with LV diameters that indicated mild dilatation versus 2) patients with moderate to severely increased LV diameters [study groups: normal vs. increased LV diameters (≥ 3.5 cm/m²)]. For analyses on the LV mass, we compared two groups as well: 1) patients with normal LV masses or with masses that indicated mild hypertrophy versus 2) patients with moderate to severely increased LV masses [study groups: normal vs. increased LV masses (males: ≥ 132 g/m²; females: ≥ 109 g/m²)].

Statistical analysis

Statistical analyses were performed with IBM SPSS statistics software (version 22, IBM Corp., Armonk, NY, USA). Categorical data are expressed as numbers (percentages). Continuous baseline variables are expressed as means \pm standard deviations. The VF waveform characteristics are presented as medians (interquartile ranges (IQRs)) and were compared using the Mann Whitney U test. A p-value of <0.05 was considered statistically significant. To provide an indication whether the effect of the LV diameter and mass on the outcomes measures was independent of other factors, we performed multivariate linear regression analyses using data of surface ECG-lead I. This lead was chosen in view of the similarity with the paddle-ECG recorded during resuscitations. The

Table 1
Clinical characteristics of patients with normal and increased LV diameters.

	Normal LV diameter n = 151	Increased LV diameter n = 40	P-value
Age (yrs)	63 ± 12	62 ± 14	0.663
Male gender	123 (82)	22 (55)	0.001
Hypertension	61 (41)	14 (35)	0.515
Diabetes	36 (24)	9 (23)	0.843
Atrial fibrillation	50 (33)	10 (25)	0.326
Previous MI	89 (59)	22 (55)	0.653
BMI (kg/m ²)	27 ± 4	25 ± 4	0.039
Secondary prevention	59 (39)	4 (10)	0.001
CRT-D	44 (29)	17 (43)	0.107
LVEF (%)	38 ± 14	28 ± 9	<0.001
LVIDd-index (cm/m ²)	2.8 ± 0.3	3.8 ± 0.3	<0.001
LV mass index (g/m ²)	110 ± 29	132 ± 30	<0.001
QRS duration (ms)*	112 (94–122)	111 (102–125)	0.374
QTc duration (ms)*	455 (423–483)	455 (423–480)	0.968
Creatinine (μmol/l)	97 ± 54	137 ± 211	0.249
Beta blocker	137 (91)	37 (93)	1.000
ACE inhibitor/ARB	129 (86)	38 (95)	0.173
Aldosterone blocker	59 (39)	20 (50)	0.224
Diuretics	69 (46)	28 (70)	0.007
Antiplatelet	91 (61)	20 (50)	0.224
Anticoagulation	66 (44)	16 (40)	0.650
Cholesterol reducer	100 (67)	28 (70)	0.690
Amiodarone	20 (13)	3 (8)	0.419

*In the absence of a typical bundle branch block. Values are n (%), means ± standard deviations or medians (IQRs). ACE inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, CRT-D: cardiac resynchronization therapy defibrillator, LV: left ventricular, LVEF: left ventricular ejection fraction, LVIDd: left ventricular internal diastolic diameter, MI: myocardial infarction.

mean amplitude and AMSA were log-transformed to approximate a normal distribution. All confounding variables as well as variables which have previously been associated with the outcome measure of interest were offered to the models [16–18].

Results

Study group

A total of 337 adults underwent a first left-sided ICD implantation with defibrillation testing during the study period. In total, 144 patients were excluded for the following reasons: no analysable 12-lead ECG of the induced VF (n = 131), missing echocardiographic data (n = 13). Accordingly, a total of 193 patients were included in the present analysis. Baseline characteristics did not differ between the in- and excluded patient groups (Supplementary Table 1).

Patient characteristics

The mean age was 63 years ± 13 and 76% (146/193) was male. Mean left ventricular ejection fraction (LVEF) was 36% ± 14. In total 58% (111/193) of patients had a previous MI, of which 41% (46/111) was located in the anterior wall and 45% (50/111) in the inferior wall. Of the patients without infarction (n = 82), LV dysfunction was caused by cardiomyopathies, hypertension or valvular heart diseases in 89% (73/82). Four percent (3/82) had a cardiac channelopathy and 7% (6/82) could not be classified. Further clinical characteristics are summarised in Tables 1 and 2.

VF characteristics in relation to the LV diameter

Measurements of the LV diameter were available for 191 patients. In total, 79% (151/191) had a normal to mildly abnormal indexed LV diameter, with a mean of 2.8 ± 0.3 cm/m². In the 21% (40/191) with a moderate to severely abnormal LV diameter, the

Table 2
Clinical characteristics of patients with normal and increased LV masses.

	Normal LV mass index n = 120	Increased LV mass index n = 57	P-value
Age (yrs)	62 ± 13	63 ± 13	0.618
Male gender	96 (80)	37 (65)	0.030
Hypertension	47 (40)	25 (44)	0.582
Diabetes	29 (24)	13 (23)	0.820
Atrial fibrillation	34 (28)	22 (39)	0.170
Previous MI	71 (59)	31 (54)	0.548
BMI (kg/m ²)	27 ± 5	27 ± 3	0.975
Secondary prevention	46 (38)	13 (23)	0.041
CRT-D	32 (27)	23 (40)	0.066
LVEF (%)	38 ± 13	33 ± 13	0.018
LVIDd-index (cm/m ²)	2.9 ± 0.4	3.3 ± 0.5	<0.001
LV mass index (g/m ²)	98 ± 19	147 ± 23	<0.001
QRS duration (ms)*	112 (94–124)	108 (101–123)	0.769
QTc duration (ms)*	450 (421–480)	466 (445–502)	0.010
Creatinine (μmol/l)	91 ± 38	127 ± 178	0.149
Beta blocker	108 (91)	52 (91)	0.919
ACE inhibitor/ARB	105 (88)	52 (91)	0.549
Aldosterone blocker	52 (44)	26 (46)	0.811
Diuretics	59 (50)	33 (58)	0.301
Antiplatelet	74 (62)	28 (49)	0.100
Anticoagulation	50 (42)	25 (44)	0.817
Cholesterol reducer	78 (66)	37 (65)	0.934
Amiodarone	13 (11)	7 (12)	0.791

*In the absence of a typical bundle branch block. Values are n (%), means ± standard deviations or medians (IQRs). ACE inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, CRT-D: cardiac resynchronization therapy defibrillator, LV: left ventricular, LVEF: left ventricular ejection fraction, LVIDd: left ventricular internal diastolic diameter, MI: myocardial infarction.

mean LVIDd index was 3.8 ± 0.3 cm/m². Baseline characteristics are presented in Table 1.

Frequency characteristics

In patients with an increased LV diameter, the dominant and median frequencies were significantly lower when compared to the subset with a normal diameter in all analysed ECG-leads (Fig. 1).

Amplitude characteristics

The mean VF amplitude and AMSA did not differ between patients with normal and increased LV diameters. This held true for all analysed ECG-leads (Fig. 1).

The bandwidth did not differ between study groups in any lead either.

Multivariate analysis

After correction for the LV mass, amiodarone and a previous MI, we found an independent association between the LV diameter and the dominant and median frequencies of VF [β −0.324 (95% CI −0.565 to −0.083) p = 0.009; β −0.291 (95% CI −0.513 to −0.069) p = 0.010].

VF characteristics in relation to the LV mass

Measurements of the LV mass were available for 177 patients. In total, 68% (120/177) had a normal to mildly abnormal indexed LV mass, with a mean of 98 ± 19 g/m². In the 32% (57/177) of patients with a moderate to severely abnormal LV mass, the mean mass index was 147 ± 23 g/m². Baseline characteristics are presented in Table 2.

Frequency characteristics

The dominant and median frequencies did not differ between study groups, with the exception of a significantly lower domi-

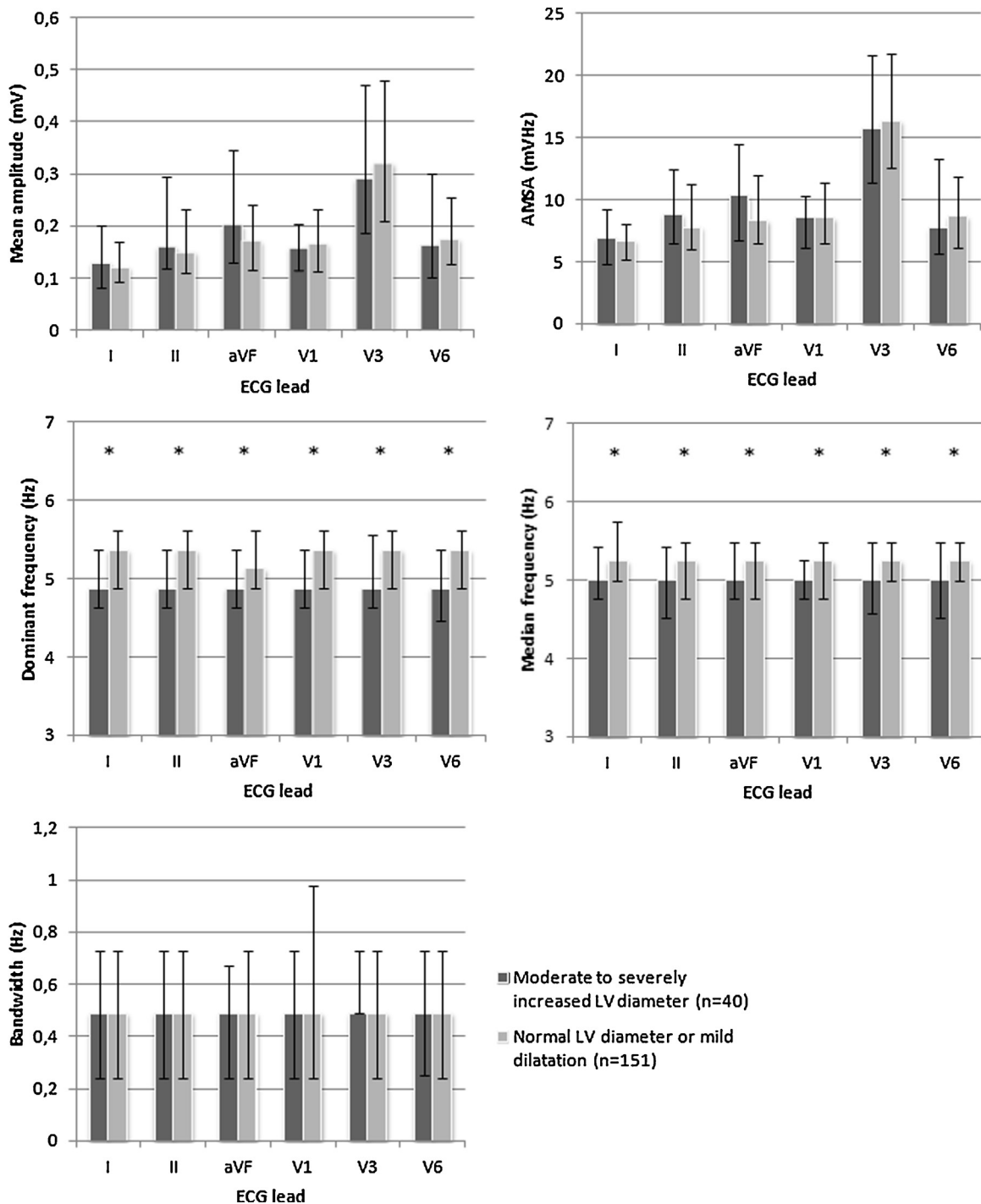


Fig. 1. Impact of the LV diameter on VF waveform characteristics of the surface ECG.

VF waveform characteristics are presented as medians with interquartile ranges. * P-value < 0.05. The dominant and median frequencies were significantly lower in patients with an increased LV diameter when compared to those with a normal LV diameter. P-values dominant frequency: lead I: 0.006, lead II: 0.010, lead aVF: 0.019, lead V1: 0.028, lead V3: 0.050, lead V6: 0.009. P-values median frequency: lead I: 0.008, lead II: 0.028, lead aVF: 0.032, lead V1: 0.027, lead V3: 0.017, lead V6: 0.006. The mean amplitude, AMSA and bandwidth did not differ significantly between patients with increased and normal LV diameters, in all leads (p-values > 0.05). AMSA: Amplitude Spectrum Area, Hz: Hertz, LV: left ventricular, mV: millivolt.

nant frequency in lead V3 in the subset with an increased LV mass compared to those with a normal LV mass (Fig. 2).

Amplitude characteristics

In patients with an increased LV mass, the mean VF amplitude was significantly higher in leads I, aVF and V3 when compared to the subset with a normal LV mass (Fig. 2). In leads II and V6, the mean amplitude was slightly higher as well (p < 0.1), but this did

not reach statistical significance. No difference was observed in lead V1. In case of an increased LV mass, the AMSA was significantly higher in leads I and V3 as well. In leads II and aVF, the AMSA was also slightly higher (p < 0.1). No difference was observed in lead V1 and V6.

The bandwidth did not differ between study groups in any lead either.

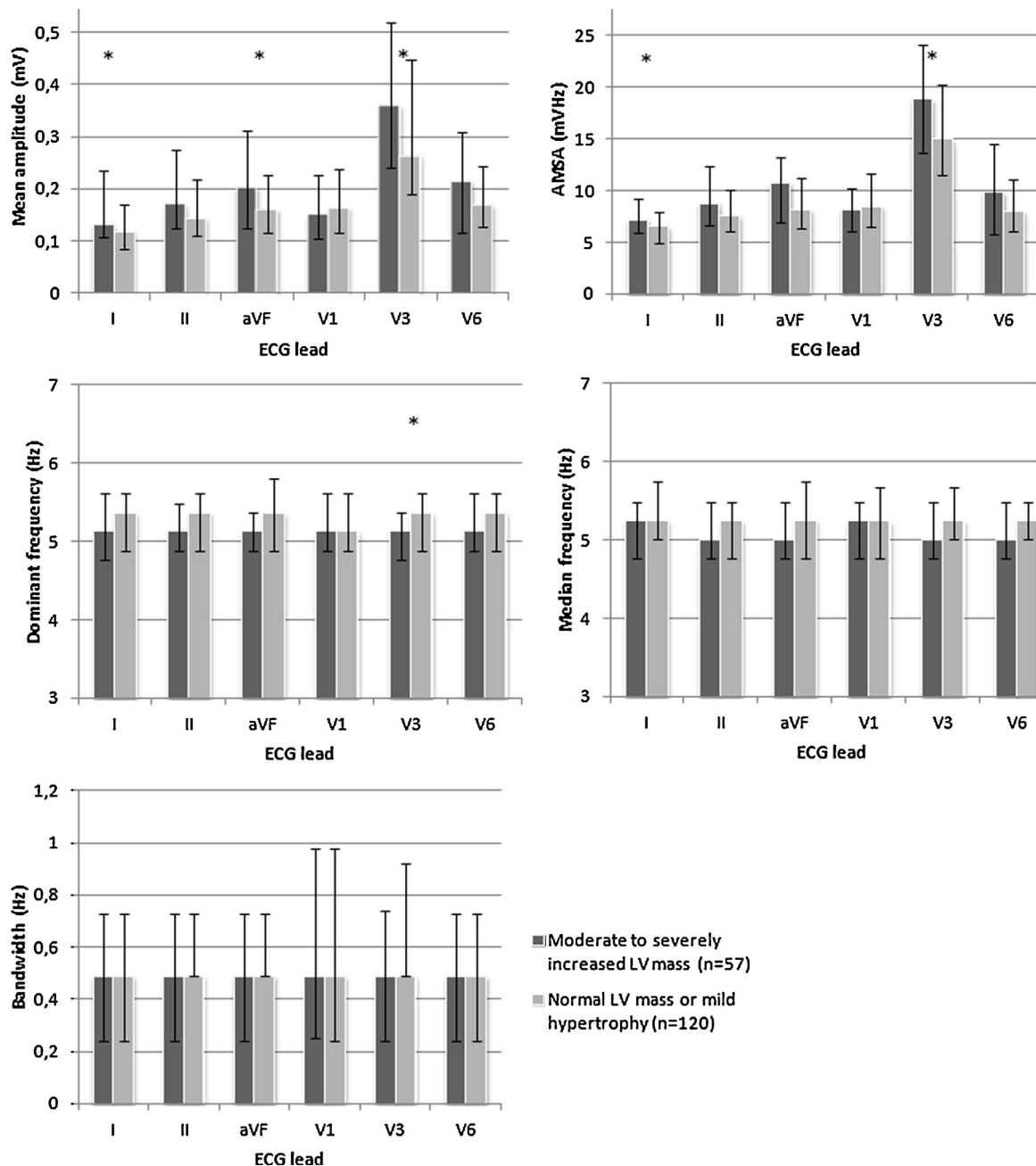


Fig. 2. Impact of the LV mass on VF waveform characteristics of the surface ECG.

VF waveform characteristics are presented as medians with interquartile ranges. * P-value < 0.05. The dominant and median frequencies as well as the bandwidth did not differ between study group, in all leads (p-values > 0.05), with the exception of the dominant frequency in lead V3 (p = 0.047). The mean amplitude and AMSA were significantly higher in patients with an increased LV mass compared to those with a normal LV mass in leads I, aVF and V3 and leads I and V3, respectively. P-values mean amplitude: lead I: 0.021, lead II: 0.050, lead aVF: 0.031, lead V1: 0.451, lead V3: 0.014, lead V6: 0.092. P-values AMSA: lead I: 0.047, lead II: 0.084, lead aVF: 0.060, lead V1: 0.282, lead V3: 0.009, lead V6: 0.144. AMSA: Amplitude Spectrum Area, Hz: Hertz, LV: left ventricular, mV: millivolt.

Multivariate analysis

After correction for a previous MI, gender and the LVEF, we observed an independent association between the LV mass and the log-transformed mean amplitude and AMSA [β 0.095 (95% CI 0.027–0.163), p = 0.006; β 0.065 (95% CI 0.008–0.122) p = 0.026].

Discussion

Frequency characteristics of initial VF varied according to the LV diameter, with consistently lower values in all ECG-leads in patients with marked LV dilatation. Amplitude characteristics were not

related to the LV diameter. In contrast, VF frequency was not related to the LV mass. While amplitude characteristics seemed higher in case of an increased LV mass, this was not consistent across all the different ECG-leads. These findings add to the growing body of evidence indicating that the VF waveform of the surface ECG is altered by pre-existent disease-related changes of the myocardium, including abnormal geometrics and infarcted areas [17,18]. In this light, a more comprehensive concept of VF characteristics seems warranted, which may contribute to renewed insights into the potential of VF analysis to guide resuscitative interventions.

Table 3

Impact of patient-related factors on ECG characteristics of the VF waveform. In this Table, we provide an overview of the currently available knowledge on associations between myocardial disease, medication and arrest variables on the one hand and VF waveform characteristics (i.e. amplitude, frequency) on the other hand from studies with patients.

	Measures related to the VF cycle length	Measures related to the VF amplitude
Acute myocardial infarction [13–15]	=	↓/=
Previous myocardial infarction [13,16–18,22]	↓/=	↓
Increased LV diameter [17]	↓	=
Increased LV mass	=	↑/=
Low LV ejection fraction [33]	↓	Unk
Beta blockers [28]	↓	Unk
Class III anti-arrhythmic drugs [17]	↓	=
Longer arrest duration [34,35]	↓	↓
CPR [36,37]	↑	↑

CPR: cardiopulmonary resuscitation, LV: left ventricular, unk: unknown, VF: ventricular fibrillation.

Determinants of the VF waveform

Animal studies

Studies in animals have generated a valuable amount of information on determinants of the VF waveform [5,10–12,23–26]. Initial studies primarily focused on the relation with markers of the metabolic state, e.g. arrest duration or coronary perfusion pressure [23–26]. More recent studies showed that the presence of an *acute* MI also results in less coarse VF [10,11]. For a history of a previous myocardial infarction, thus for *pre-existent* infarction as well, it has been demonstrated that the course of the VF waveform differs when compared to VF in a structurally normal heart [11,12].

Human studies

In Table 3, we provide an overview of our current knowledge on patient-related factors that influence the electrocardiographic appearance of the VF waveform. Among the different studies on the impact of a *previous* MI, data are consistent, demonstrating lower VF amplitude characteristics in the leads adjacent to the area of infarction [13,16–18]. In contrast, results of the studies on *acute* MI yielded contrasting findings in the setting of OHCA [13–15]. Despite the frequent occurrence of LV dilatation and hypertrophy, and the associated increased risk of sudden cardiac death, the impact of the LV diameter and mass on VF characteristics has so far only scarcely been studied [27].

Impact of the LV diameter and mass

LV diameter

The dominant and median frequencies were consistently lower in all analysed ECG-leads in case of an increased LV diameter. This effect was seen in both patients with and without pre-existent infarctions and was independent of other variables that are known to lower VF frequency characteristics (Table 3), as for example amiodarone and beta blocker use [28]. The dominant frequency roughly corresponds to the number of fibrillation cycles per second and to the reciprocal of the cycle length [29]. In animal hearts, it has been demonstrated that acute ventricular stretching results in shortening of the action potential duration and refractory period, leading to higher dominant frequencies [30,31]. This seems contrasting with our observations. However, acute stretching may not mimic the human situation in which LV remodelling is often multifactorial and results from longstanding adaptation to cardiac overload. In animal hearts, it has been demonstrated that in case of heart failure remodelling, the VF rate decreases [31]. The latter is in concordance with our observations and corresponds to the characteristics of our study population, which mainly consists of heart failure patients. A mapping study in explanted hearts from transplant recipients with dilated cardiomyopathy provides further insight in the potential underlying mechanism of the altered VF frequency characteristics [32]. In this study, it was observed that

areas of fibrosis on histopathologic examination corresponded with areas of conduction block during VF.

LV mass

Observations with regard to the LV mass were less consistent, although it seems that an increased LV mass is associated with higher VF amplitudes. Previously, we have shown that in the presence of pre-existent infarction, and thus with a loss of depolarizing mass, VF amplitude characteristics were lower in the adjacent leads [18]. The present observations seem in line with these findings as with an increased cell mass amplitude characteristics were generally higher, although findings were not as robust and consistent as observed for the correlation between LV dilatation and the VF waveform. This may relate to local differences in wall thickness adjacent to the various ECG leads. Unfortunately, our imaging information was limited to echocardiography and lacks an advanced technique like MRI. This could have provided important information on the complex alterations in ventricular architecture that occur with remodelling resulting in coexistence of regions of fibrosis and adaptive hypertrophy.

Implications

The present study further completes the current picture with regard to the impact of pre-existent myocardial disease on characteristics of the VF waveform. It needs to be determined whether our findings on short-duration electrically-induced VF also apply to the OHCA setting. If this is the case, our findings may have important implications. First, pre-existent myocardial changes may then complicate the use of the VF waveform as a mere proxy of arrest duration or actual metabolic state. As such, it may influence the predictive ability for shock success and outcome. For example, low amplitude, low frequency VF could represent someone with a long arrest duration, but could also be indicative of pre-existent myocardial pathology (prior infarction, LV dilatation etc.). Second, it could explain the contrasting observations in studies that reported on the impact of acute infarction on the VF waveform. In these studies, factors like previous infarction, LV mass or diameter were not accounted for. Third, it should be noticed that the observed interplay between the VF waveform on the one hand, and pre-existent and acute myocardial pathology on the other, is dependent on the ECG-recording direction. Concluding, our findings support the idea that the appearance of the VF waveform on the surface ECG depends on multiple factors. In this light, more comprehensive studies on VF characteristics are warranted to investigate if and how VF-guided resuscitation strategies might improve outcome after cardiac arrest.

Limitations

First, although the present study question was retrospectively defined, data are part of a prospective study project on VF waveform analysis [18]. This explains the lack of echocardiographic data in 13 cases, which resulted in exclusion for this paper. Our project is performed in a specialised research electrophysiology lab, which accounts for the fact that this study represents only about half of our total of ICD implantations. However, as baseline characteristics of the other half of patients did not differ (Supplementary Table 1), it is unlikely that exclusion of patients has affected our main findings. Second, in view of the low number of patients with an increased LV mass, we were unable to perform in-depth analysis on a potential gender-dependent relation between LV mass and VF waveform characteristics. In this context, we used a guideline-defined categorisation, and corrected for gender in multivariate analysis. Finally, in- and exclusion of patients with channelopathies did not result in different study findings.

Conclusions

Frequency characteristics of the VF waveform were consistently lower across all ECG-leads in case of an increased LV diameter, with no effect on amplitude characteristics. In contrast, VF frequencies did not vary according to the LV mass. While less uniform, amplitude-related measures were slightly higher in case of an increased LV mass. Further study on pre-existent disease-related myocardial characteristics that modulate the VF waveform is warranted to improve our insights into factors which should be accounted for in future studies on VF-guided resuscitative interventions.

Conflicts of interest

Prof. De Boer is a member of the European advisory board on interventional cardiology of Medtronic.

J.L. Bonnes, J. Thannhauser, J. Nas, S.W. Westra, R.M.G. Jansen, G. Meinsma, J.L.R.M. Smeets, W. Keuper and M.A. Brouwer have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2017.03.029>.

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